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The Evaluation of Maternal and Perinatal Results in Pregnant with Sickle Cell Anemia

Orak Hücreli Anemili Gebelerde Maternal ve Perinatal Sonuçların Değerlendirilmesi

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ABSTRACT

Objective: Although most pregnancies having Sickle Cell Anemia (SCA) result in live births, they pose increased risks for fetal and maternal complications. The purpose of the present study was to examine maternal and fetal complications in pregnant women with SCA and in those who are SCA carriers. **Material and Methods:** In our study, 34 pregnant women with sickle cell anemia, 38 pregnant women with SCA carriers, and 46 healthy pregnant women who were followed up in our hospital between January 2016 and 2022 were evaluated retrospectively. Pregnant's age, gestational week, hemogram values, birth weight, delivery method, birth week, 1-5. Minute APGAR-scores were compared between groups. **Results:** Hemoglobin levels of pregnant with SCA or carriers were found to be significantly lower than healthy pregnant women ($p<0.05$). Birth weight in healthy pregnant women was found to be significantly higher than in pregnant with sickle cell anemia and carriers ($p<0.05$). The number of transfusions and cesarean sections in the SCA-group was found to be significantly higher than the other groups ($p<0.05$). The presence of pyelonephritis and pulmonary embolism in the SCA-group was found to be significantly higher than the other groups ($p<0.05$). Intrauterine growth retardation and Abruptio placentae was found to be significantly higher in the SCA-group compared to the other groups ($p<0.05$). **Conclusion:** Pregnancies diagnosed with SCA are in the high-risk group and should be followed up in experienced centers. Clinicians should be careful about possible complications and keep in mind that these complications may cause maternal mortality.

Keywords: Pregnancy; pulmonary embolism; pyelonephritis; sickle cell anemia

ÖZET

Amaç: Orak hücreli anemi tanılı gebeliklerin çoğunluğu canlı doğumla sonuçlansa da, bu gebeliklerde fetal vexmaternal komplikasyonlar açısından yüksek risk bulunmaktadır. Bu çalışmadaki amacımız, orak hücrelixanemili gebelerde ve orak hücrelixanemi taşıyıcılığı olan gebelerde maternal vexfetal komplikasyonları değerlendirmektir. **Gereç ve Yöntemler:** Çalışmamızda Ocak 2016-2022 arasında hastanemize başvuran ve takipleri yapılan; orak hücreli anemili 34 gebe, orak hücreli anemi taşıyıcısı 38 gebe ve 46 sağlıklı gebe retrospektif olarak değerlendirilmiştir. Gebelerin yaş, gebelik haftası, hemogram değerleri, doğum ağırlığı, doğum şekli, doğum haftası, 1-5. Dakika APGAR skorları gruplar arasında karşılaştırılmıştır. **Bulgular:** Orak hücreli anemisi olan veya taşıyıcı olan gebelerin hemoglobin seviyeleri sağlıklı gebelere göre anlamlı düşük saptanmıştır($p<0.05$). Sağlıklı gebelerde doğum ağırlığı, orak hücreli anemisi olan ve taşıyıcılığı olan gebelere göre anlamlı yüksek saptandı($p<0.05$). SCA grubunda transfüzyon ve sezaryen sayısı diğer gruplara göre anlamlı olarak yüksek bulundu ($p<0,05$). SCA grubunda piyelonefrit ve pulmoner emboli varlığı diğer gruplara göre anlamlı olarak yüksek bulundu ($p<0.05$). SCA grubunda intrauterin gelişme geriliği ve Abruptio plasentae diğer gruplara göre anlamlı olarak daha yüksek bulundu ($p<0,05$). **Sonuç:** Orak hücreli anemi tanılı gebelikler yüksek risk grubunda olup deneyimli merkezlerde takip edilmelidir. Klinisyenler olası komplikasyonlar konusunda dikkatli olmalı ve bu komplikasyonların maternal mortaliteye neden olabileceği akılda tutmalıdır.

Anahtar Kelimeler: Gebelik; orak hücreli anemi; pulmoner emboli; pyelonefrit

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Sickle Cell Anemia (SCA) is the most prevalent severe hemoglobinopathy and is one of the most prevalent single-gene abnormalities on a global scale.[1] The disease affects 3 million people every year and more than 300.000 children are born with it.[1] Dramatic improvements in the survival rates of individuals diagnosed with SCA in affluent nations over the past 40 years have led to the need to evaluate SCA again as a long-term ailment with far-reaching consequences on adult health.[1] SCA is a hereditary autosomal-recessive disease developing after homozygosity for Hemoglobin S (HbS), which has an abnormal hemoglobin structure.[2] This disease occurs when valine takes the place of glutamic acid, which is the sixth amino acid in the hemoglobin beta globin chain. An insoluble hemoglobin tetramer ($alpha^2/betaS^2$) occurs in the deoxygenated state in SCA.[3] It is already known that pregnancy is linked with an elevated risk of problems related to Sickle Cell in mothers and fetuses in pregnant with SCA.[4,5] Although most pregnancies with maternal SCA result in live birth, there is an elevated risk for fetal and maternal complications.[5,6] Two recently published meta-analyses that compiled the findings of comparative research that focused on the relationship between SCA and pregnancy reported that pregnancies complicated by SCA had a four-fold higher risk of stillbirth.[7,8] These reviews also reported a two- to four-times higher incidence of preterm birth, preeclampsia, and Small for Gestational Age (SGA) fetuses in pregnancies with SCA.[7,8] A significant part of the complications occurs as a result of increased metabolic demand, hypercoagulability, and vascular stasis during pregnancy. Patients who are diagnosed with SCA and who want to become pregnant must be evaluated preconceptionally and informed of genetic counseling because of the complications during pregnancy.[9] Contradictory results were reported in previous studies that were conducted on pregnant women with SCA. It was reported in some of these studies that fetal outcomes were good, and maternal complications increased. Some studies also reported both fetal and maternal complications.[10] Pregnant women who have SCA have an increased risk of maternal mortality, sepsis, increased transfusion need, pneumonia, asymptomatic bacteriuria, genitourinary infection, and Deep Vein Thrombosis.[11] A higher risk of intrauterine growth retardation, preeclampsia, eclampsia, preterm labor, and abruptio placentae is also detected in pregnancy outcomes of patients who have SCA.[12] However, it was also noted that many previous studies had poor methodological quality, lacked information provided about the clinical management of SCA, were unable to classify their results according to SCA genotypes, and had difficulties in explaining the confusion according to maternal characteristics.[8] The Royal College of Obstetricians and Gynecologists (RCOG) of the United Kingdom released a guide in 2011 on the management of SCA in pregnancy.[13] This recently updated guide forms the basis of the best care practice in the UK, and partner maternity clinics recommend multidisciplinary care with prophylactic folic acid, penicillin, and low-dose aspirin to decrease the infection risk. The scarcity of up-to-date data regarding the outcomes of pregnant who have SCA in the UK means that the extent to which the heightened hazards associated with SCA in pregnancy have been lessened during the last ten to fifteen years is unclear.[14,15] SCA is considered the most prevalent hereditary hemoglobinopathy in Türkiye.[16] The high prevalence of sickle cell anemia in our country may make this disease a public health problem that needs to be examined carefully.[16] Our current research will contribute to the optimal management of these patients. The purpose of this research is to investigate maternal and fetal complications in pregnant women with SCA and SCA carriers.

MATERIALS AND METHODS

Among the patients who applied to our hospital's Obstetrics Clinic from January 2016 to January 2022 and underwent pregnancy follow-up, those who got diagnosed with Sickle Cell Anemia (SCA) or a diagnosis of SCA carrier were scanned retrospectively from the hospital database in the present research. Totally 34 pregnant who were diagnosed with Sickle Cell Anemia, 38 patients who were diagnosed as Sickle Cell Anemia carriers, and 46 healthy pregnant women were included in the research. All selected patients consist of patients diagnosed in the hematology department of our hospital. The pregnant women in the

control group consist of pregnant women without known hematological disease who were followed up in our polyclinic during the same period. Those who had regular follow-ups during pregnancy and adhered to the optimal treatment schedule were added in the research. Those who were followed up in an external center or who did not have optimal patient compliance and did not comply with the medication schedule despite being followed by us were not included in the study. Daily low molecular weight Heparin (LMWH) was administered as standard treatment for prophylactic anticoagulation according to the RCOG Guide from pregnancy confirmation until the 36th week of gestation. Many women needed temporary blood transfusions during pregnancy because of clinical manifestations (e.g., severe anemia or sickle cell crisis). Individuals with a history of poor obstetric care or repeated pregnancies were given a prophylactic transfusion. After pregnancy was confirmed, preventive penicillin therapy and folic acid (5 mg/day) were given. The 38th and 40th weeks were used for the induction of labor (or, if required, an elective cesarean section) due to the higher chance of stillbirth. During the postpartum period, non-steroidal anti-inflammatory drugs were the recommended treatment for discomfort. The ages, gestational weeks, number of pregnancies, and medication history of the patients were recorded along with their frequency of antenatal hospitalization. The hemogram values, number of transfusions during pregnancy, maternal complications (anemia, pyelonephritis, preeclampsia, pulmonary embolism, death), and fetal complications (intrauterine growth retardation, preterm labor, membrane rupture, death, *abruptio placentae*), birth weeks, delivery methods, birth weights, 1st and 5th minute APGAR scores of the participants were also compared. The statistical analysis of the data was performed by using the SPSS-20 (IBMxSPSS, IBM Corporation, Armonk, NY, USA). The Shapiro Wilk test was used to investigate whether the distribution of continuous variables was close to normal. Continuous variables were shown as mean±standard deviation. Kruskal Wallis H test was applied to examine the significant difference between 3 continuous variables that did not show normal distribution. Descriptive statistics of categorical data are presented as number (n) and percentage (%). For proportion comparisons and association studies between categorical variables, the chi-square test or Fisher's exact test was used, depending on the number of samples. The p-value considered statistically significant was <0.05. The study was designed in line with the Declaration of Helsinki Principles. Informed consent forms were obtained from the patients in the present study and the rules regarding animal rights were followed. The study was started after receiving ethics committee approval from Dokuz Eylul university with decision number 2023/39-10 dated 06/12/23.

RESULTS

A total of 118 patients were included in the study. Totally 34 pregnant who were diagnosed with Sickle Cell Anemia (SCA), 38 patients who were diagnosed as Sickle Cell Anemia carriers, and 46 healthy pregnant women were included in the research. The average age of patients who were diagnosed with Sickle Cell Anemia (SCA) was 24.1±3.5, the average age of patients with SCA carriers was 24.6±3.7, and the average age of healthy pregnant women was 24.2±4.1, and the difference between the samples was not significant (p:0.26). The gravida number of patients who were diagnosed with SCA was 2.9±0.8, the gravida number of patients who were diagnosed as being SCA carriers was 2.9±1.1, and the gravida number of healthy pregnant women was 3.2±0.7, and the difference between the samples was not significant (p:0.46). The parity number of the patients who were diagnosed with SCA was observed to be 2.3±0.9, the parity number of those diagnosed as SCA carriers was 2.5±1.1, and the parity number of the healthy pregnant women was 2.9±0.6, and the difference between the samples was not significant (p:0.54). The gestational week of those who were diagnosed with SCA was 37.5±1.4, the gestational week of patients who were diagnosed as SCA carriers was 37.9±1.6, and the gestational week of healthy pregnant women was 38.2±1.4, and the difference between the samples was not significant (p:0.36). When the transfusion numbers were evaluated, 2 of 46 healthy pregnant women (4.3%), 4 of 38 pregnant women diagnosed as SCA carriers (10.5%), and 5 of 34 pregnant women who were diagnosed with SCA (14.7%)

received a transfusion and the number of transfusions was seen to be significantly higher in the SCA Group ($p<0.05$). The hemoglobin levels of the pregnant women who were diagnosed with SCA were found to be 8.4±1.6 (g/dL), the hemoglobin levels of those who were carriers of SCA were 9.3±1.3 (g/dL), and the hemoglobin levels of the healthy pregnant women was 11.6±1.5 (g/dL). The hemoglobin levels of the pregnant women who were diagnosed with SCA and SCA carriers were found to be significantly lower than those of the healthy pregnant women ($p<0.05$). The differences between the groups were not significant with respect to 1st minute and 5th minute apgar scores (p:0.55, p:0.61 respectively). A total of 13 (38%) of the patients who were diagnosed with SCA gave birth by cesarean section, 10 (26.3%) of the SCA carriers and 12 (26%) of the healthy pregnant women gave birth by cesarean section. The cesarean section rate was found to be significantly higher in those who were diagnosed with SCA ($p<0.05$). Previous cesarean section indication (57%), cephalopelvic disproportion (17.1%), fetal distress (14.2%), non-progressive labor (5.7%), and breech presentation (5.7%) were detected in cesarean section indications and 91.4% of the pregnant women received spinal anesthesia and the rest received general anesthesia. When the birth weights were compared, it was found to be 2850±220 g in the anemia group, 3030±290 g in the carrier sample, and 3320±440 g in the Healthy Pregnancy Group, and birth weight was significantly higher in healthy pregnant women ($p<0.05$) (Table 1).

Maternal and fetal mortality was not detected in the three samples. Although pyelonephritis was detected in 3 patients (8.8%) in the SCA Group, it was not detected in the pregnant women in the other groups and the difference between the samples was significant in this regard ($p<0.05$). Preeclampsia was detected in 1 (2.1%) patient in the Healthy Pregnancy Sample, in 1 (2.6%) patient in the SCA Carrier Sample, and 2 (5.8%) patients in the SCA Sample, and the difference between the samples was not significant (p:0.48). Although Pulmonary Embolism was not detected in the healthy pregnant women and the SCA Carrier Sample, it was detected in 2 (5.8%) patients in the SCA Sample, and the difference between the samples was significant in this regard ($p<0.05$). Intrauterine Growth Retardation was detected in 1 patient (2.1%) in the Healthy Pregnancy Sample, in 1 (2.6%) patient in the SCA Carrier Sample, and 3 (8.8%) patients in the SCA Sample, and the difference between the samples was significant in this regard ($p<0.05$). Membrane rupture was detected in 3 patients (6.5%) in the Healthy Pregnancy Sample, in 2 patients (5.2%) in the SCA Carrier Sample, and 2 patients (5.8%) in the SCA Sample, and the difference between the samples was not significant in this regard (p:0.36). Preterm labor was experienced in 2

TABLE 1: The demographic and clinical data of the patients.

	Healthy Pregnant Women n:46	SCA Carrier n:38	SCA n:34	p
		Mean±SD		
Age	24.2±4.1	24.6±3.7	24.1±3.5	0.26
Gravida	3.2±0.7	2.9±1.1	2.9±0.8	0.46
Parity	2.9±0.6	2.5±1.1	2.3±0.9	0.54
Pregnancy Week	38.2±1.4	37.9±1.6	37.5±1.4	0.36
Hemoglobinx (g/dL)	11.6±1.5	9.3±1.3	8.4±1.6	<0.05
1stmMinute Apgar Score	7.8±1.3	7.9 ± 1.1	7.6±1.2	0.55
5th minute Apgar Score	8.4±1.2	8.5±1.1	8.2±1.3	0.61
Birth weight (g)	3320±440	3030±290	2850±220	<0.05
		n (%)		
Number of transfusions	2 (4.3%)	4 (10.5%)	5 (14.7%)	<0.05
Number of Caesarean Sections	12 (26%)	10 (26.3%)	13 (38%)	<0.05

*SCA: Sickle Cell Anemia

patients (4.3%) in the Healthy Pregnancy Sample, in 2 patients (5.2%) in the SCA Carrier Sample, and 2 patients (5.8%) in the SCA Sample, and the difference between the samples was not significant in this regard (p:0.47). Although abruptio placentae was not experienced in the healthy pregnant women and the SCA Carriers, it was experienced in 2 patients (5.8%) in the SCA Sample and was significantly higher ($p<0.05$) (Table 2).

DISCUSSION

In our study, the hemoglobin levels of pregnant women diagnosed with Sickle Cell Anemia (SCA) and SCA carriers were significantly lower than those of healthy pregnant women. The number of transfusions in the SCA Group was significantly higher than the carrier group and the healthy group. The cesarean section rate in those diagnosed with Sickle Cell Anemia was found to be significantly higher than other groups. Birth weight in healthy pregnant women was significantly higher than other groups.

When the data of our study were evaluated, it was found that the risk of pyelonephritis, pulmonary embolism, Intrauterine Growth Retardation, and abruptio placentae was higher in pregnancies diagnosed with SCA than in the pregnant females with SCA and healthy pregnancies. Maternal mortality did not occur in the study group. We think that the use of low molecular weight Heparin (LMWH) line with the guidelines was effective in preventing it. Contradictory results were reported in international studies conducted on pregnant women diagnosed with or carrying SCA. Although increased perinatal and maternal morbidity and mortality were reported in low-income countries, it was emphasized that perinatal outcomes were positive and maternal complications were quite low in high-income countries.[17] In a study conducted by Kurt et al., it was reported that perinatal outcomes in pregnant women diagnosed with SCA were similar to healthy pregnant women, but maternal death and pyelonephritis were detected more frequently in pregnant women diagnosed with SCA.[18] In our study, although there was no significant difference between the groups in terms of maternal deaths, pyelonephritis was higher in the SCA group. The fact that no risk was detected in terms of maternal deaths in our study can be explained by the improvement of treatment and care conditions in the perinatal and postnatal periods. In a study that was conducted with 1526 pregnant women, it was reported that an increase was detected in the incidence of obstetric hemorrhage, Deep Vein Thrombosis, pulmonary embolism, sepsis, pneumonia, and transfusion in pregnant women who were diagnosed with SCA.[19] In our study, similar to this study, the number of pulmonary embolisms and transfusions was significantly higher in the SCA group (sepsis, pneumonia, and Deep Vein Thrombosis were not evaluated in our study). In another study that included 17.952 pregnant women, the risk of maternal mortality, increased cerebral vein thrombosis, postpartum infection, sepsis, transfusion, Deep Vein Thrombosis, pyelonephritis, pneumonia, and systemic inflammatory response syndrome were reported.[11] Although there was no significant difference in terms of maternal death in our study, Cerebral Vein Thrombosis and systemic inflammatory response syndrome were

TABLE 2: The data on maternal and fetal complications.

	Healthy Pregnant Women n %	SCA Carriers n %	SCA n %	p
Pyelonephritis	0(0%)	0(0%)	3 (8.8%)	<0.05
Preeclampsia	1(2.1%)	1(2.6%)	2(5.8%)	0.48
Pulmonary Embolism	0(0%)	0(0%)	2(5.8%)	<0.05
Intrauterine Growth Retardation	1(2.1%)	1(2.6%)	3 (8.8%)	<0.05
Membrane rupture	3(6.5%)	2(5.2%)	2(5.8%)	0.36
Preterm labor	2(4.3%)	2(5.2%)	2 (5.8%)	0.47
Abruptio placentae	0(0%)	0(0%)	2 (5.8%)	<0.05

*SCA: Sickle Cell Anemia

not detected. Frequent pregnancy follow-up in our country may have made it possible to prevent these complications. However, the limited number of patients may have resulted in this result. In a study conducted by Villers et al., it was also reported that cesarean section rates were higher in pregnant women with SCA, and the risk of pregnancy-related preeclampsia, detachment, intrauterine growth retardation, antepartum hemorrhage and premature birth was high.[11] Similarly, in our study, cesarean section rates, intrauterine growth retardation, and abruptio placentae were higher in the anemia group, but no differences were observed with regard to preterm labor. It was found in our study group that in pregnant with SCA, the rates of maternal complications were comparable to those of healthy pregnant women; however, pyelonephritis and pulmonary embolism were more common in pregnant with SCA. Supervisory of pregnant females who are diagnosed with SCA must be carried out by a multidisciplinary team. It is already known that the main causes of maternal mortality in pregnancies diagnosed with SCA are pulmonary embolism, bleeding, and infection. In a previous study conducted by El-Shafei et al., 5 of 12 maternal deaths in pregnant women were associated with pulmonary embolism.[20] The reason for the high complication rates in this study may be the demographic structure of the region and the lack of follow-up. However, in another study, no increased incidence of embolism was reported in pregnant women who were sickle cell carriers.[21] This result may be caused by the fact that only carriers were evaluated in this study. In the literature, it is recommended to initiate low-dose Aspirin in pregnant females with SCA to decrease the incidence of preeclampsia and to use LMWH in pregnant women who have thrombosis risk factors.[22] Risk factors are listed as previous history of Venous Thromboembolism, family history of Venous Thromboembolism, parity, advanced age, obesity, immobility, multiple pregnancies, sepsis, and dehydration. No maternal mortality was detected in our research group, and the main reason for this was considered to be the low molecular weight of Heparin (LMWH). According to the 2009 Guide of the Royal College of Medicine in the UK, it was stated that pregnant women who were diagnosed with SCA had a moderate risk for thrombosis and embolism and LMWH can be administered, and we comply with and support this procedure.[23] In our study, similar to other studies in the literature, an increased need was found for transfusion in the anemia group.[24] Since the most important side effect of the disease is bone marrow suppression, it is possible that this result will be similar in all studies in the literature. The main limitation of the study is that it was designed retrospectively. At the same time, the limited number of patients in the study limits the ability to adequately evaluate complications in pregnant women diagnosed with sickle cell anemia. Since the incidence of sickle cell anemia is observed to be higher in our country, the strength of the study is that it sheds light on the complications of the disease in pregnancy and raises awareness among physicians in this regard.

CONCLUSION

Although individuals who were diagnosed with SCA used to die at an early age in the past, the number of patients who reach reproductive age and want to become pregnant is increasing today with the increase in life expectancy. Pregnancies diagnosed with SCA are in the high-risk group and should be followed up in experienced centers. Clinicians should be careful about possible complications and keep in mind that these complications may cause maternal mortality. This approach should result in early identification and management of acute problems by the appropriate physicians in the appropriate place. Our results highlight the importance of multidisciplinary perinatal care, ongoing studies to target SCA, and increased public health efforts to reduce disparities in pregnancy-related outcomes for women with SCA.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ufuk Atlıhan;* ***Design:*** *Onur Yavuz;* ***Control/Supervision:*** *Mehmet Güney;* ***Data Collection and/or Processing:*** *Eyüp Özgözen;* ***Analysis and/or Interpretation:*** *Begüm Ertan;* ***Literature Review:*** *Ufuk Atlıhan;* ***Writing the Article:*** *Onur Yavuz;* ***Critical Review:*** *Ufuk Atlıhan.*

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